Physiological Basis for the Treatment Of Intractable Asthma*

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SOME years ago Dr. Chevalier Jackson coined a phrase which has become a medical cliche: "All is not asthma that wheezes." He implied that much wheezing goes on that is not asthma. To this the author would like to take exception. To the practicing physician everything that wheezes is asthma. To him, asthma means wheezing. Wheezing means bronchial obstruction. Therefore, asthma and bronchial obstruction are synonymous.

Bronchial obstruction may be due to many causes — new growths, congenital abnormalities, foreign bodies, swelling of the bronchial mucosa, mucous secretions, bronchospasm and so on. New growths, congenital abnormalities and foreign bodies may in themselves cause mechanical obstruction. Swelling of the bronchial mucosa, mucous secretions and bronchospasm are usually secondary obstructions.

The bronchi respond to irritation with a defense mechanism. The purpose of this mechanism is to prevent the entrance of noxious agents, or to dilute or get rid of them. In the lower respiratory tract this reaction represents what laryngospasm represents in the upper respiratory tract, namely, a protective mechanism. In the lower respiratory tract it is characterized by bronchospasm, the outpouring of mucous and coughing.

This protective mechanism can be initiated by an allergic reaction, an infectious reaction or a mechanical one. No matter which it is, we call it bronchial asthma. In other words, all asthma is the result of obstruction of the respiratory tract. But the initiating cause may come from a mechanical factor — as a growth — or it may come from an irritating stimulus, allergic, infectious or otherwise.

Many irritants may set off the asthmatic defense pattern. Two, however, are most common: One, the allergic antigen-antibody reaction and, two, infection. The allergic reaction is by far the most common, so common in fact that the term bronchial asthma is too often taken to mean only allergy. It was this unfortunate identification that impelled Jackson to coin his famous phrase implying that, to many people, wheezing means only one thing — allergic asthma. In allergic asthma the antigen-antibody reaction acts as the precipitating irritant which sets off the bronchial defense mechanism. In infectious asthma the asthmatic response is due to the infection *per se* which acts as the precipitating irritant setting off the defense mechanism in the same way that allergy does. It is not set off by an allergy to the bacteria causing the infection.

Infection may cause asthma in any age group. But among older people the onset of pulmonary emphysema creates an added susceptibility to infection. When pulmonary emphysema is present, it not only impairs respiration, it also impairs the ability of the bronchi to rid themselves of secretions and debris. This increases the susceptibility to recurrent and chronic infection. Infection destroys the ciliated epithelium of the bronchial mucosa. It also makes the bronchial walls thick and rigid. Thus a functional bronchiectasis is produced. The accumulation of foreign matter may then act as an irritant, precipitating the asthmatic attack.

Among younger people, the same sequence of events may follow. But the development of pulmonary emphysema comes not as the result of senile changes but as the result of persistent allergic asthma. In other words, allergic asthma often produces irreversible pulmonary emphysema. The allergy may then disappear. The emphysema, however, persists and becomes responsible for the asthmatic attack. Actually, the allergy has become a part of the past history. It no longer functions as the present cause.

THEORY OF NEUROSIS

Even though both allergy and infection may call forth an asthmatic response, it is well known that many individuals have respiratory allergy or infection, or both, and yet do not have asthma. Coughing is their only response to irritation. For this difference between individuals there is no satisfactory organic interpretation. An interpretation is offered, however, by the psychoanalytic theory of neurosis. Detailed psychoanalytic studies of asthmatics have led to the conclusion that the asthmatic attack is a sort of substitute for an inhibited or repressed cry of anxiety or rage. It is often a cry to gain affection from a denying and rejecting mother. A person chooses the asthmatic pattern for the expression of his emotional conflict, probably either because of a constitutional determinant or because of conditioning by one or more episodes of organic bronchial obstruction.

The obstruction which produces the wheezing dyspnea in bronchial asthma is caused by three factors acting singly or in common. These are bronchospasm, plugging by mucous secretion and edema of the bronchial mucosa. At the beginning of the attack bronchospasm appears to play the most important obstructing role. As the attack progresses mucous plugs and bronchial edema assume the more important obstructing roles.

As obstruction sets in a series of related physiologic disturbances develop. These are progressive and self-propagating and result in a vicious spiral which may end in death. The first of these disturb-

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ances is the development of a marked increase in negative intrapleural pressure during inspiration. This creates a sucking action on the capillaries of the bronchi, causing the development of bronchial edema. Meanwhile pulmonary emphysema develops with flattening of the diaphragm, diminution in vital capacity and increase of residual air. These interfere with the respiratory exchange and add to the anoxemia. Anoxemia produces anoxia, particularly of the medullary respiratory center. The patient then becomes dyspneic. His respiration is labored. As a result he is concerned only with getting his breath and fears to take time out to drink. At the same time the labor of breathing causes a profuse outpouring of sweat. Furthermore, the drugs taken for relief are often diuretic. These three factors—water deprivation, excessive sweating and diuresis—cause hemoconcentration. Hemoconcentration not only adds to the anoxia, it also causes the mucous secretion in the bronchi to become thick and viscid, further increasing bronchial obstruction.

Simultaneously with the development of anoxemia and anoxia there is an excessive accumulation of carbon dioxide. In consequence the oxygen dissociation curve is changed so that tissue anoxia is further increased. The excessive accumulation of carbon dioxide, the lack of oxygen and the effect of depressant drugs may make the medullary respiratory center completely inactive. Respiration is then carried on only by anoxic stimulation of the carotid body and aortic chemoreceptor centers. When these become depressed, death from respiratory failure results.

RESPONSE TO EPINEPHRINE

This rather brief summary of the pathological physiology of bronchial asthma clarifies several diagnostic and therapeutic observations concerning the development and course of an asthmatic attack. For example, we know that many patients when seen early in an attack of asthma or in a mild attack respond almost miraculously to an injection of 1/1000 epinephrine. On repeating the injection its action may become more and more transitory and ineffective. The patient has become epinephrine-fast. Many explanations have been given for the development of this state—among others, that a tolerance to epinephrine has been established; i.e., that bronchospasm is no longer relieved by epinephrine. Since this is contrary to what has been found in the experimental laboratory the only logical conclusion that can be drawn is that the patient has passed the stage where his bronchial obstruction is primarily due to bronchospasm and has reached the stage of bronchial obstruction due to mucous plugging and bronchial edema. Further administration of epinephrine at this stage is not only futile but even harmful. The observation that after a period of withdrawal epinephrine may again become effective does not mean that epinephrine reactivity has been regained but that the bronchial obstruction is again due chiefly to bronchospasm.

With the development of epinephrine-fastness we may conclude that the bronchial obstruction is due chiefly to mucous plugging or bronchial edema. Treatment must then be directed toward the relief of one or the other of these conditions. If the mucous that is coughed up is seen to be thick and tenacious and if in addition we find evidences of hemoconcentration, such as a high red cell count and high hemoglobin value, we may conclude that mucous plugging is probably the chief cause of the bronchial obstruction. Treatment is then directed toward the relief of hemoconcentration. This may be accomplished by the administration, by intravenous drip, of 5 per cent glucose in normal saline, which should be repeated or continued until such time as the red cell count and hemoglobin concentration have reached normal values. Glucose is used to combat the acidosis which accompanies any prolonged attack of asthma and normal saline is used to make up the electrolyte lost by the excessive perspiration and diuresis. To aid further in thinning down of the bronchial mucous, sodium iodide may be added to the intravenous drip.

IMPROVEMENT WITH RELIEF OF HEMOCONCENTRATION

As hemoconcentration is relieved the patient begins to cough up more and more plugs of mucous and generally within 48 hours has recovered from his acute attack. Meanwhile for immediate relief during episodes of acute exacerbations of dyspnea, 0.5 gm. of aminophylline may be administered intravenously or per rectum. Despite some evidence that aminophylline acts as a broncho dilator, its efficiency seems to lie chiefly in relieving fatigue of the medullary respiratory center, for many patients feel relieved after the administration of aminophylline yet show little if any change in the respiratory tracings taken before and after such administration. At this point it is also well to warn that aminophylline may act more as a diuretic than as a central stimulant. On occasion it has been known to cause such great diuresis that despite the administration of as much as five liters of intravenous fluids the hemoconcentration has not been relieved. Therefore, the blood must be frequently examined to determine the state of hemoconcentration.

Occasionally, despite disappearance of hemoconcentration the patient is not relieved and may not cough up any thick mucous plugs, in fact may cough up large amounts of thin, frothy sputum. We may then presume and perhaps confirm by bronchoscopic examination that the cause of the bronchial obstruction is bronchial edema. Under these circumstances the administration of 50 per cent glucose intravenously is indicated and often gives prompt relief.

RESPIRATORY DEPRESSANT DRUGS

A fundamental understanding of the mechanism of bronchial asthma is useful not only for preventive, curative and palliative treatment but also for avoiding improper treatment, treatment detrimental to the welfare of the patient.

The most serious menace to the welfare of the asthmatic patient is the depression of his respira-

tory center. With the development of anoxia the center becomes increasingly vulnerable to respiratory depressant drugs.

It is common practice to give such drugs to patients in an asthmatic attack. This is often necessary and justifiable if they are intended to relieve the asthmatic attack. The distinction is made on the basis of the dosage required for the relief of each condition. It takes a larger dose of a respiratory depressant drug or a more powerful drug to relieve an attack of asthma than it does to relieve fatigue or nervousness. With the respiratory center already depressed by a lack of oxygen and without any means of measuring the degree of depression, it becomes unsafe to attempt to relieve the asthma by this means. The powerful respiratory depressants such as the opium derivatives should never be used and the less powerful depressants such as the barbiturates should be used with infinite caution and only in small dosages. The anesthetics have no place in the treatment of the asthmatic attack, since they depress the respiratory center and, if used in effective dosage, inhibit the cough reflex which is so essential to the clearing of the bronchi.

In spite of all these strictures against respiratory depressants in the treatment of the asthmatic attack, many will cite experiences of their successful use. To this there is but one answer, that the drugs were given at a time when regardless of dosage or the type of drug used the respiratory center was not sufficiently depressed to be adversely affected. It is probably true that in many cases such treatment can be safely given but since we cannot always identify the patient or attack in which it is safe to administer a respiratory depressant and since measures which do not use respiratory depressants are effective, it would seem the better part of caution to avoid their use. Death in bronchial asthma should occur only from complications. It should never occur from the administration of drugs which are intended to prevent it.

Few asthmatics die without the aid of a doctor. The patient's panic often engulfs the doctor. He is then willing to try anything instead of using forbearance and caution and a continuous observation of the individual and his attack.

SUMMARY AND CONCLUSIONS

1. Bronchial asthma means bronchial obstruction regardless of the cause.

2. Bronchial obstruction calls forth a defense response, the abnormal respiratory pattern known as bronchial asthma.

3. The most common stimulants calling forth this defense mechanism are allergy and infection.

4. The bronchial obstruction produced by the defense mechanism is due to bronchospasm, mucous plugging and bronchial edema.

5. These lead to anoxemia, anoxia, dehydration and respiratory depression.

6. A proper appreciation of the physiological pathology underlying each of these conditions is the only basis for proper therapy of bronchial asthma.

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